IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

HOW BIG OF A ROLE DO GENES PLAY IN ANOREXIA?

Arushi Basu
IBDP, Podar International School
Mumbai, India

Abstract: The paper covers the genetic mechanisms, that lead to anorexia nervosa development. Anorexia is a complex eating disorder with life-threatening implications and a high fatality rate. The physiological impact of AN includes bone mineral density loss and heart problems such as bradycardia. Beauty standards and the media, for example, significantly impact the risk of developing eating disorders. The research highlights the importance of genetic factors in AN, notably Neuronatin (NNAT), Histone Deacetylase 4 (HDAC4), Estrogen-Related Receptor Alpha (ESRRA), Single Nucleotide Polymorphisms (SNPs), 5-Hydroxytryptamine Receptor 1D (HTR1D), and opioid receptor delta (OPRD1). These genes' interactions and their effects on hormone control, metabolism, and central nervous system function are being studied. Investigating genes and biological factors in anorexia nervosa is crucial for comprehending the mechanisms underlying the disorder and developing improved treatments. Although genes cannot predict the development of anorexia, they do have the potential to enhance the diagnosis and treatment of anorexia, thereby saving lives and reducing relapse rates.

IndexTerms **– Anorexia Nervosa, Eating Disorders, Genetic factors, Biological factors**

INTRODUCTION

Eating disorders (ED) rank among the top 10 leading causes of disability among young women, and anorexia nervosa has the highest mortality rate of all mental disorders [1]. The DSM-V defines Anorexia Nervosa (AN) as the restriction of energy intake relative to requirements, resulting in abnormally low body weight for the patient's age, sex, developmental trajectory, and physical health. AN is associated with distorted body image, an intense fear of gaining weight or becoming fat, or persistent behaviour that interferes with weight gain. Feelings of being disturbed by one's body weight or shape, having one's self-worth dictated by body weight or shape, and a persistent lack of recognition of the seriousness of low body weight and emaciation are also common.

Prevalence is the proportion of cases in the population present at a specific point or interval. According to research, the prevalence of eating disorders has been increasing, with East Asia and South Asia experiencing the highest burden.[2] Research analysing 94 studies with accurate ED diagnoses found the weighted mean of lifetime prevalence (prevalence at any point of time) of eating disorders to be 8.4% (ranging from 3.3% to 18.6%) among women and 2.2% (ranging from 0.8% to 6.5%) among men globally. These findings highlight the significant presence of eating disorders in the population and the need for attention and support in addressing these conditions. Whereas the lifetime prevalence of anorexia was reported 0.1% to 3.6% in females and 0% to 0.3% in males.[3] The prevalence rates of anorexia tend to be relatively low compared to other eating disorders. This could suggest that fewer people are being diagnosed or that they are not receiving an accurate diagnosis.

Mortality is the measure of the frequency of occurrence of death in each country or geographic area. Mortality in AN is amongst the highest of all psychiatric disorders, with suicide being one of the leading causes of death. A study conducted by Runfola CD, et al., [4] showed the prevalence of suicide attempts in patients diagnosed with AN was 9.2%. According to the Interpersonal Theory of Suicide, an individual must be fearless about death and have an increased endurance to pain to be capable of attempting suicide [5]. Many studies have shown that patients with eating disorders are generally known to have decreased pain sensitivity, which might increase self-harm and suicide risk [6]. These findings highlight that the mortality rate in anorexia nervosa is high, with suicide being a leading cause of death, potentially linked to decreased pain sensitivity.

Being a life-threatening disorder, AN has serious consequences. The physical effects of anorexia can be severe, such as loss of bone mineral density (BMD). During a person's teenage years and twenties, their BMD naturally increases until they reach peak bone mass density (PBM), the amount of bony tissue at the end of skeletal maturation. As previously mentioned, anorexia involves calorie restriction, which reduces one's bone mass and hence results in the development of fragile, brittle bones which are key features of osteoporosis. Although osteoporosis is not fatal itself, hip fractures can lead to permanent disability or even death. Hip fractures are fatal because the body faces challenges in generating new bones. J Scott et al. [7] discovered that women with low bone density are at an increased risk of hip fracture. It is important to know that currently, there is no known cure for osteoporosis.

Due to self-induced starvation, the body enters a hibernation state to save energy. This is a physiological adaptation by our bodies to survive harsh conditions. This causes low metabolic activity and a decrease in the heart rate. Sinus bradycardia, characterized by an abnormally low heart rate, is one of the most common cardiovascular complications among patients with AN. Unlike BMD, bradycardia is curable and with proper treatment is reversible, but it is important to note that in some cases bradycardia may necessitate the implantation of a permanent pacemaker [8, 9].

AN cannot be disassociated from sociocultural factors. Global societal standards promoting extreme thinness as the epitome of female beauty adversely affect youngsters, leading to body dissatisfaction, disordered eating, and low self-esteem. Diverse and inclusive beauty representations are essential for healthier body image and self-acceptance. The famous Playboy magazine has been associated with influencing the "ideal" body size for both men and women. [10] In this age of globalization where beauty standards rapidly travel across the globe, it is easy for adolescents to get influenced by such ideals.

The prominent objectification of the female body, social media, and unrealistic social norms increases the risk of developing eating disorders among women. The constant change in the beauty industry adversely affects the mindset of an individual if they do not fit into these unnatural beauty standards. Various factors, including media, advertising, beauty standards, and social interactions, actively contribute to the objectification of the female body by teaching girls and women that their value primarily lies in their looks and emphasizing the importance of pursuing attractiveness. A study conducted by Alison E. et al [11] found that children aged 9 to 14 who were trying to look like same-sex figures in the entertainment media were more likely to become concerned with their diet than their peers. There is a lot of stigmas surrounding mental illnesses, especially eating disorders, especially in racial/ethnic minorities. More acculturated people were more likely to have eating difficulties, while less acculturated people were less likely to have gotten treatment for eating disorders as seen in a case study by Fary M et al. [12] Many go undiagnosed due to cultural differences in help-seeking behaviors, stigma, and a lack of awareness among healthcare providers. This leads to delayed or inadequate treatment.

Men can encounter comparable challenges regarding body image. However, most research measures utilized in clinical practice and research to assess eating disorder-specific psychopathology were originally developed and normed for female samples. This disparity diminishes the likelihood that men receive appropriate treatment for their eating disorders. Hence, men with eating disorders face a double disadvantage when compared to women with comparable problems. [13] Unlike women, who seek a thin body image, men prefer a muscular body image. A study was designed to evaluate men's worries about muscularity in the development of the Swansea Muscularity Attitudes Questionnaire. The findings indicate that males will engage in activities that increase their muscularity because they perceive muscularity to increase their sense of masculinity, confidence, and attractiveness. [14] Anorexia nervosa has historically been considered a predominantly female disorder, resulting in a lack of focus on male experiences. This underrepresentation can lead to biased findings and an incomplete understanding of the unique challenges faced by men with anorexia. Therefore, AN in men does not present similarly to AN in women, which can complicate men's abilities to get treatment.

But at an age where almost all children are exposed to sociocultural factors, why does only a small percentage of them develop an eating disorder? This could reflect that eating disorders might not have an entirely environmental basis. Instead, other factors could induce the onset of an eating disorder.

But what are these additional factors? Genetics could play a significant role in this. The etiology of anorexia nervosa (AN) involves a complex interplay between genetics and unique environmental factors. A twin study by Wade et al. [15] found that genetics contribute to about 58% of the variance in anorexia nervosa (AN), highlighting its significant heritability. However, approximately 42% of the variance is influenced by unique environmental factors emphasizing the interplay between genetics and the environment in the development of AN. While environmental factor does play a significant role, it is crucial to acknowledge the contribution of genetic factors in understanding the underlying mechanisms of anorexia.

Researchers have attempted to understand the causes and factors for anorexia by focusing on environmental, sociocultural, and familiar factors but there has been limited research done in the field of biological risk factors despite the high rate of heritability. To date, several genes have been linked to AN. This includes NNAT, HDAC4, ESRRA SNPs, HTR1D and OPRD1 and serotonin genes. Below, we discuss each of these genes and how well they have contributed to understanding AN from a genetic perspective.

BODY

Biological factors such as hormones, neurological pathways, and genes contribute to the development of eating disorders. Biological factors are often underestimated in their contribution. Stewart et al. [16] conducted a study that demonstrated the tendency of the general population to downplay the significance of biological factors in the development of anorexia nervosa. Anorexia nervosa doesn't have clear biological markers like some other medical conditions, so it has been mainly seen as a psychological disorder influenced by things like body image issues and sociocultural pressures. Because these factors are easier to observe and measure, they have received more attention in research and treatment. However, understanding the biological factors is crucial as although biological factors cannot accurately predict the onset of an illness, they help us unravel the underlying mechanisms of the disorder, leading to more effective treatment options.

Research has shown that the heritability of eating disorders does not follow a traditional Mendelian pattern in which a single gene can accurately predict the onset of AN. Rather, it involves the interaction of multiple genes and their complex interplay with environmental factors. A wide range of protein-coding genes has been identified as being involved in the hereditary aspects of the disorder.

Neuronatin or NNAT is one of the genes which may be responsible for the inheritance of anorexia. NNAT is involved in brain development, encoding a proteolipid which controls ion channels during brain development. It is an imprinted gene which is only expressed from the paternal allele. A study by Lombardi et al [17] did an exome analysis of two different families including female as well as male individuals who were diagnosed with anorexia. The researchers found mutations in NNAT in both probands (a person serving as the starting point for the genetic study of a family), suggesting a potential link between NNAT and the development of anorexia in both. To confirm this data, researchers screened a group of eight male and 144 female patients with AN, and 11 NNAT variants were discovered, indicating that 40.00% and 6.25% of male and female persons, respectively, carried an NNAT variant. It is important to note that not all individuals with AN necessarily have the same genetic variations or mutations.

Additionally, there is a connection between NNAT and the pituitary gland. It is assumed to play a role in its development and maturation. The pituitary gland secretes several hormones, including growth hormone (GH), prolactin (PRL), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH). Each of these hormones is expressed by the NNAT gene, according to research [18]. Anorexia is frequently linked to hormonal abnormalities.[19] TSH levels over normal are known to restrict food intake. When injected centrally into rats, it has been proven to lower food intake [20]. A malfunction or improper development of the pituitary gland because of NNAT may trigger hormonal imbalances that may lead to a reduced appetite. It should be noted that our current understanding of the relationship between the NNAT gene, pituitary gland function, and hormonal regulation is still evolving. Further research is necessary to establish a more definitive and comprehensive understanding of this area.

Recently, the histone deacetylase 4 (HDAC4) gene have been observed in multiple studies related to AN. The HDAC4 is a transcriptional repressor, which turns off other genes. This gene encodes the protein for making the histone deacetylase 4. This enzyme is involved in various processes, including the development, and functioning of the central nervous system (CNS), as well as bone, muscle, and metabolism regulation [21]. A study conducted by Michael Lutter et al. [22] focused on investigating the relationship between the HDAC4 gene and the risk of developing an eating disorder (ED) in mice. To investigate the effects of a specific genetic variant, the researchers studied mice with HDAC4 mutation who were bred to have a consistent genetic background. When these mice were given a high-fat diet, male mice showed a slight decrease in weight gain compared to normal mice, while female mice did not. In terms of behaviour, male mice with the variant spent less time eating and showed reduced motivation to work for rewarding food. They also exhibited a decrease in activity during specific periods of the day. On the other hand, female mice with the variant displayed social subordination when tested in a tube dominance test (particularly social dominance through the measurement of aggression), while male mice did not show this behaviour. Since HDAC4 is known to control memory and learning [23] we can gain new knowledge about the neurological basis of an AN. These findings provide insights into how this genetic variant may affect weight gain, eating behaviour, and social interactions in mice.

Another study by Huxing Cui et al. focuses on ESRRA (estrogen-related receptor alpha) and its relation to anorexia. ESRRA encodes ERRα, a nuclear receptor similar to estrogen receptors, involved in regulating energy balance and metabolism. This study used a combination of exome sequencing, whole-genome sequencing, and linkage analysis to investigate the genetic factors underlying the recurrence of eating disorders, particularly anorexia nervosa, in two families. In the first family, a specific change in the ESRRA gene was present in all affected family members. In the second family, a harmful mutation in the HDAC4 gene was reported. Moreover, the researchers found that ESRRA and HDAC4 interact with each other, both in living organisms (in vivo) and in laboratory settings (in vitro). However, they also discovered that HDAC4 can reduce the activity of ESRRA-induced target genes. It does this by a process called deacetylation, which "turns off" the activity of these target genes. When HDAC4 is active, it can inhibit or suppress ESRRA-induced genes. These findings suggest that the specific genetic changes or variations identified in the ESRRA and HDAC4 genes might lead to a decrease in the activity of ESRRA. This decrease in activity could potentially increase the chances of developing anorexia nervosa.[24]

The fourth type of gene commonly studied in relation to anorexia nervosa is single nucleotide polymorphisms (SNPs). SNPs are naturally occurring genetic variations found throughout an individual's DNA. On average, they appear approximately once every 1,000 nucleotides, indicating that a person's genome can contain around 4 to 5 million SNPs. Scientists have identified over 600 million SNPs in populations worldwide. The variant must be present in at least 1% of the population to be classified as an SNP. Laramie Duncan et al. [25] performed a genome-wide association study to investigate the genetic basis of AN and its potential correlations with psychological, educational, and metabolic traits. The study examined the heritability of SNPs using a sample of 3,495 AN cases and 10,982 controls. The researchers analyzed 10,641,224 SNPs and insertion-deletion variants with minor allele frequencies greater than 1%. The results of this study revealed a heritability estimate of 0.20 (SE=0.02) for AN, indicating that a significant proportion of the heritability observed in twin studies can be attributed to common genetic variations. Additionally, positive genetic correlations were observed between AN and other conditions such as schizophrenia, neuroticism, educational attainment, and high-density lipoprotein cholesterol. These findings suggest potential shared genetic factors or biological pathways between AN and these phenotypes.

However, it is worth noting that a study conducted by K. Wang et al. [26] yielded different results regarding the significance of single nucleotide polymorphisms (SNPs) in the context of anorexia nervosa (AN). Despite using a substantial number of SNP markers, specifically over 598,000, none of the SNPs analyzed in that study met the strict criteria for genome-wide significance.

A study conducted by A. W. Bergen et al. [27] explored the involvement of HTR1D (5-Hydroxytryptamine Receptor 1D) and OPRD1 (opioid receptor delta 1) genes, which are associated with the serotonergic and neurotransmitter systems, respectively. The researchers employed various analytical techniques, including sequence variation analysis, linkage analysis, and association analysis, utilizing datasets consisting of both families and case-control groups. Through their investigation, they identified both new and pre-existing single nucleotide polymorphisms (SNPs) within the HTR1D and OPRD1 genes. Significant associations between specific SNPs in HTR1D and OPRD1 and AN were observed suggesting a potential role of these genes in the development of the

disorder. Another study found 3 SNPs to be associated with both restricting anorexia nervosa and binge-purge AN within the gene for OPRD1. An association between 2 polymorphisms within HTR1D and RAN was also found. [28]

These genes are part of the complex network of neurotransmitter systems, particularly the serotonergic and opioidergic pathways, which play crucial roles in regulating various physiological and psychological processes. The serotonin system, being involved in mood regulation and the stress response, can be influenced by chronic stress, potentially leading to alterations in appetite regulation and the development of AN. Serotonin, also known as 5-hydroxytryptamine (5-HT), is critical in regulating various physiological and psychological functions necessary for survival. These functions include food intake regulation, prevention of depressive states, control of anxiety, fear etc. An increase in 5-HT neurotransmission can lead to symptoms resembling those observed in anorexia nervosa such as reduced eating behavior [29] The HTR1D gene is responsible for encoding the serotonin 1D receptor. A study conducted by Brown et al. [30] identified abnormalities within the HTR1D gene in individuals with AN. These findings suggest that genetic variations or anomalies in the HTR1D gene may contribute to the dysregulation of the serotonin system and potentially play a role in the development of AN.

DISCUSSION

The role of genes in anorexia nervosa is complex and not yet fully understood. Current research has explored various genes and their potential involvement in the development of anorexia nervosa, but specific genes that predispose individuals to the disorder have not been definitively identified. Studies investigating the genetic factors of anorexia nervosa have faced challenges, including the lack of comprehensive phenotyping.

Anorexia is a complex disorder with several subgroups and symptoms. Although genetic studies frequently focus on broad diagnostic criteria, the underlying genetic variables may differ across anorexia nervosa subgroups or symptoms. Failure to take this heterogeneity into account might hide important genetic variants. The connections between genes and the environment are frequently overlooked in most investigations. This may hinder our comprehension of the disorder's complexities. Therefore, these differences in phenotypes make it challenging to identify common genetic factors across individuals with anorexia.

Despite these challenges, several studies have conducted genome-wide analyses to identify candidate genes that may be associated with anorexia nervosa though these findings have not been consistently replicated in independent studies. The present review discusses the findings and potential roles of genes such as NNAT, HDAC4, ESRRA, SNPs, HTR1D and OPRD1. NNAT is involved in brain development and may affect hormonal regulation, including the pituitary gland. Variants in the HDAC4 gene have been associated with altered weight gain, eating behavior, and social interactions in mice. Changes in the ESRRA gene, along with its interaction with HDAC4, may decrease the activity of ESRRA and increase the risk of developing anorexia. SNPs showed positive genetic correlations have been observed between anorexia and other conditions such as schizophrenia and educational attainment. Specific SNPs within these genes, which are associated with the serotonergic and neurotransmitter systems, have been found to be significantly associated with anorexia nervosa.

Despite these findings, several unanswered questions and potential research directions remain. Firstly, it is crucial to investigate the involvement of NNAT in brain development, particularly its role in encoding a proteolipid that regulates ion channels during brain development, highlighting its significance in shaping neuronal function and connectivity. Additionally, further exploration of the relationship between NNAT, the pituitary gland, and hormone regulation is needed to gain a better understanding of these complex interactions which could lead to targeted therapeutic interventions in the future. Hormonal imbalance has been observed as a significant feature in individuals with anorexia. It is important to note that hormones regulate gene expression and can regulate gene expression by triggering alterations in enzyme patterns within target cells through the synthesis of specific RNA molecules, while it's the gene that provides instruction for making these hormones. For example, let us consider Thyroid Stimulating Hormone (TSH) gene. Mutations in this gene can disrupt the production of TSH, which is responsible for regulating the thyroid gland. Consequently, individuals with such mutations may experience thyroid-related disorders, including abnormal metabolism and potential growth and development issues. The interrelationship between hormones and genetic factors is an important aspect to consider when studying any disorder.

While the study conducted by Michael Lutter et al. provides valuable insights into the potential role of the histone deacetylase 4 (HDAC4) gene in eating disorders, several limitations and drawbacks should be considered. Firstly, the study was conducted using mice as a model organism. Although animal models provide a valuable platform for studying complex biological processes, it is important to acknowledge that findings from mice may not directly translate to humans. The genetic and physiological differences between mice and humans can limit the generalizability of the results and their applicability to human eating disorders. Also, anorexia in humans involves complex psychological and emotional factors, such as distorted body image and cognitive processes, which are crucial to understanding and treating the disorder. Mice, although they show altered feeding behaviors, lack the cognitive and psychological complexities seen in human anorexia nervosa experiences. The observed differences between male and female mice indicate a potential gender-specific effect of HDAC4 gene variations however it did not extensively investigate the underlying mechanisms responsible for these differences. Elucidating the molecular pathways and biological processes involved would provide a more comprehensive understanding of the gene's role in eating disorders.

It is important to consider the limitations of SNPs. They exhibit population-specific characteristics, resulting in variations in their frequencies and associations with traits among different populations. While Laramie Duncan et al.'s study found a positive association between SNPs and AN, K. Wang et al. found no significant link despite analyzing many SNP markers. There could have also been SNP mutations that influenced the results. These findings highlight the disorder's intricate and varied nature, implying that the genetic variables contributing to AN may be multifaceted and entail a combination of genetic variations beyond the scope of the SNPs investigated.

The study by A. W. Bergen et al. [21] primarily focused on identifying single nucleotide polymorphisms (SNPs) within the HTR1D and OPRD1 genes and their associations with AN. While significant associations were observed in control individuals, it is important to note that association does not imply causation. Additionally, the study did not extensively explore the potential interactions between these SNPs and environmental factors, which could contribute to the complex nature of AN. Furthermore, the sample size used in the study may limit the generalizability of the findings. While the researchers utilized datasets consisting of both families and case-control groups, the specific sample size and demographic characteristics are not provided. Replication of the findings in larger and more diverse populations would strengthen the validity and reliability of the results.

The mortality rate of anorexia is increasing alarmingly, while the treatments for anorexia are incompetent and individuals relapse quite often. With the help of various genetic approaches, opportunities for diagnosis and devising better treatment options may increase. Genetic predictors may aid in identifying individuals at risk of developing AN. Understanding the genetic and hormonal factors contributing to anorexia is critical for developing targeted interventions and personalized treatment approaches for early detection. Early detection and intervention are crucial for improving outcomes and preventing the progression of the disorder. Genetic markers can help identify individuals who may be more susceptible to AN.

CONCLUSION

In conclusion, anorexia nervosa (AN) is a serious psychiatric disorder with high mortality rates and significant impacts on individuals' physical and mental health. The prevalence of eating disorders, including AN, has been increasing globally, particularly in East Asia and South Asia. Sociocultural factors, such as unrealistic beauty standards and objectification of the female body, contribute to the development of eating disorders. Genetic research has shown that AN has a significant heritable component, with several genetic predictors identified. Understanding the interplay between genetic and environmental factors is crucial for developing effective prevention strategies and personalized treatment approaches for individuals with AN.

Research on the biological factors contributing to the development of anorexia nervosa (AN) has shed light on the intricate interplay between genes, hormones, and neurological pathways. While biological factors are often underestimated, understanding their significance is crucial for unravelling the underlying mechanisms of the disorder and developing more effective treatment options.

Studies have shown that AN does not follow a traditional Mendelian pattern of inheritance, but rather involves the interaction of multiple genes and their complex interplay with environmental factors. Genes such as Neuronatin (NNAT), Histone Deacetylase 4 (HDAC4), ESRRA, HTR1D, and OPRD1 have been implicated in the hereditary aspects of AN. These genes are involved in brain development, hormonal regulation, neurotransmitter systems, and energy balance, among other functions. Moreover, the findings suggest that hormonal imbalances, particularly in the pituitary gland, may be triggered by genetic variations in NNAT. The dysregulation of pituitary hormones can contribute to the hormonal disturbances observed in AN. Additionally, genetic variations in HDAC4 and ESRRA genes have been linked to altered weight gain, eating behavior, social interactions, and energy balance. Furthermore, studies have investigated single nucleotide polymorphisms (SNPs) and their associations with AN. While some studies have identified significant SNPs related to AN, others have yielded different results, highlighting the complex nature of genetic influences on the disorder.

However, it is necessary to approach the findings with caution and acknowledge the limitations of previous investigations. Although animal models and genome-wide association studies (GWAS) have produced useful insights, the translation to human populations and the functional implications of genetic variants require additional research. To enhance our understanding of the genetic makeup of AN, collaborative initiatives involving large-scale investigations, comprehensive phenotyping, and integration with environmental factors are necessary. Such efforts will facilitate the development of personalized prevention strategies and treatment approaches, ultimately leading to improved outcomes for individuals affected by this serious psychiatric disorder.

REFERENCES

[1] Striegel-Moore, R. H., & Bulik, C. M. (2007). Risk factors for eating disorders. American psychologist, 62(3), 181.

[2] Wu, J., Liu, J., Li, S., Ma, H., & Wang, Y. (2020). Trends in the prevalence and disability-adjusted life years of eating disorders from 1990 to 2017: Results from the Global Burden of Disease Study 2017. *Epidemiology and Psychiatric Sciences, 29*, E191.

[3] Marie Galmiche and others, Prevalence of eating disorders over the 2000–2018 period: a systematic literature review, *The American Journal of Clinical Nutrition*, Volume 109, Issue 5, May 2019, Pages 1402–1413

[4] Runfola, C. D., Thornton, L. M., Pisetsky, E. M., Bulik, C. M., & Birgegård, A. (2014). Self-image and suicide in a Swedish national eating disorders clinical register. *Comprehensive Psychiatry*, *55*(3), 439-449.

[5] Ribeiro, J. D., Witte, T. K., Van Orden, K. A., Selby, E. A., Gordon, K. H., Bender, T. W., & Joiner Jr, T. E. (2014). Fearlessness about death: the psychometric properties and construct validity of the revision to the acquired capability for suicide scale. *Psychological assessment*, *26*(1), 115.

[6] Papežová, H., Yamamotova, A., & Uher, R. (2005). Elevated pain threshold in eating disorders: physiological and psychological factors. *Journal of psychiatric research*, *39*(4), 431-438.

[7] Cummings, S. R., Black, D. M., Nevitt, M. C., Browner, W., Cauley, J., Ensrud, K., Genant, H. K., Palermo, L., Scott, J., & Vogt, T. M. (1993). Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. *Lancet (London, England)*, *341*(8837), 72–75.

[8] Yahalom, M., Spitz, M., Sandler, L., Heno, N., Roguin, N., & Turgeman, Y. (2013). The significance of bradycardia in anorexia nervosa. International Journal of Angiology, 22(02), 083-094.

[9] Sall, H., & Timperley, J. (2015). Bradycardia in anorexia nervosa. Case Reports, 2015, bcr2015211273

[10] Katzmarzyk, P. T., & Davis, C. (2001). Thinness and body shape of Playboy centerfolds from 1978 to 1998. *International Journal of Obesity*, *25*(4), 590-592.

[11] Field, A. E., Camargo, C. A., Jr, Taylor, C. B., Berkey, C. S., Roberts, S. B., & Colditz, G. A. (2001). Peer, parent, and media influences on the development of weight concerns and frequent dieting among preadolescent and adolescent girls and boys. *Pediatrics*, *107*(1), 54–60.

[12]Cachelin, F. M., Veisel, C., Barzegarnazari, E., & Striegel-Moore, R. H. (2000). Disordered eating, acculturation, and treatment-seeking in a community sample of Hispanic, Asian, Black, and White women. *Psychology of Women Quarterly*, *24*(3), 244-253.

[13] Edwards, S., & Launder, C. (2000). Investigating muscularity concerns in male body image: development of the Swansea Muscularity Attitudes Questionnaire. The International journal of eating disorders, 28(1), 120–124.

[14] Striegel-Moore, R. H., Leslie, D., Petrill, S. A., Garvin, V., & Rosenheck, R. A. (2000). One-year use and cost of inpatient and outpatient services among female and male patients with an eating disorder: evidence from a national database of health insurance claims. *The International journal of eating disorders*, *27*(4), 381–389.

[15] Wade, T. D., Bulik, C. M., Neale, M., & Kendler, K. S. (2000). Anorexia nervosa and major depression: shared genetic and environmental risk factors. *The American journal of psychiatry*, *157*(3), 469–471.

[16] Stewart, M. C., Keel, P. K., & Schiavo, R. S. (2006). Stigmatization of anorexia nervosa. International Journal of Eating Disorders, 39(4), 320-325.

[17] Lombardi, L., Blanchet, C., Poirier, K., Lebrun, N., Ramoz, N., Moro, M. R., ... & Bienvenu, T. (2019). Anorexia nervosa is associated with Neuronatin variants. *Psychiatric Genetics*, *29*(4), 103-110.

[18] Revill, K., Dudley, K. J., Clayton, R. N., McNicol, A. M., & Farrell, W. E. (2009). Loss of neuronatin expression is associated with promoter hypermethylation in pituitary adenoma. *Endocrine-related cancer*, *16*(2), 537–548.

[19] Bruno Estour and others, Hormonal Profile Heterogeneity and Short-Term Physical Risk in Restrictive Anorexia Nervosa, *The Journal of Clinical Endocrinology & Metabolism*, Volume 95, Issue 5, 1 May 2010, Pages 2203–2210

[20] Lin, M. T., Chu, P. C., & Leu, S. Y. (1983). Effects of TSH, TRH, LH and LHRH on thermoregulation and food and water intake in the rat. *Neuroendocrinology*, *37*(3), 206-211.

[21] Sild, M., & Booij, L. (2019). Histone deacetylase 4 (HDAC4): a new player in anorexia nervosa?. *Molecular Psychiatry*, *24*(10), 1425-1434.

[22] Davis, K. C., Saito, K., Rodeghiero, S. R., Toth, B. A., Lutter, M., & Cui, H. (2020, February 4). *Behavioral alterations in mice carrying homozygous HDAC4A778T missense mutation associated with eating disorder*.

[23] Kim, M. S., Akhtar, M. W., Adachi, M., Mahgoub, M., Bassel-Duby, R., Kavalali, E. T., ... & Monteggia, L. M. (2012). An essential role for histone deacetylase 4 in synaptic plasticity and memory formation. *Journal of Neuroscience*, *32*(32), 10879-10886.

[24] Cui, H., Moore, J., Ashimi, S. S., Mason, B. L., Drawbridge, J. N., Han, S., Hing, B., Matthews, A., M Adams, C. J., Darbro, B. W., Pieper, A. A., Waller, D. A., Xing, C., & Lutter, M. (2013). Eating disorder predisposition is associated with ESRRA and HDAC4 mutations. *The Journal of clinical investigation*, *123*(11), 4706–4713.

[25] Duncan, L., Yilmaz, Z., Gaspar, H., Walters, R., Goldstein, J., Anttila, V., Bulik-Sullivan, B., Ripke, S., Eating Disorders Working Group of the Psychiatric Genomics Consortium, Thornton, L., Hinney, A., Daly, M., Sullivan, P. F., Zeggini, E., Breen, G., & Bulik, C. M. (2017). Significant Locus and Metabolic Genetic Correlations Revealed in Genome-Wide Association Study of Anorexia Nervosa. *The American journal of psychiatry*, *174*(9), 850–858.

[26] Wang, K., Zhang, H., Bloss, C. S., Duvvuri, V., Kaye, W., Schork, N. J., Berrettini, W., Hakonarson, H., & Price Foundation Collaborative Group (2011). A genome-wide association study on common SNPs and rare CNVs in anorexia nervosa. *Molecular psychiatry*, *16*(9), 949–959.

[27] Bergen, A. W., van den Bree, M. B., Yeager, M., Welch, R., Ganjei, J. K., Haque, K., Bacanu, S., Berrettini, W. H., Grice, D. E., Goldman, D., Bulik, C. M., Klump, K., Fichter, M., Halmi, K., Kaplan, A., Strober, M., Treasure, J., Woodside, B., & Kaye, W. H. (2003). Candidate genes for anorexia nervosa in the 1p33-36 linkage region: serotonin 1D and delta opioid receptor loci exhibit significant association to anorexia nervosa. *Molecular psychiatry*, *8*(4), 397–406.

[28] Brown, K. M., Bujac, S. R., Mann, E. T., Campbell, D. A., Stubbins, M. J., & Blundell, J. E. (2007). Further evidence of association of OPRD1 & HTR1D polymorphisms with susceptibility to anorexia nervosa. *Biological psychiatry*, *61*(3), 367–373.

[29] Blundell J. E. (1986). Serotonin manipulations and the structure of feeding behaviour. *Appetite*, *7 Suppl*, 39–56. https://doi.org/10.1016/s0195-6663(86)80051-4

[30] Brown, K. M., Bujac, S. R., Mann, E. T., Campbell, D. A., Stubbins, M. J., & Blundell, J. E. (2007). Further evidence of association of OPRD1 & HTR1D polymorphisms with susceptibility to anorexia nervosa. *Biological psychiatry*, *61*(3), 367–373.